According to *Statement of Biological Deposit*, Malcolm Moos, Jr., M.D., Ph.D., an inventor of the above-identified application, stated:

1. That the following biological material referred to in the specification of this application has been deposited:

Strain	**Accession number**
HCDMP-1	PTA-2595

2. That the date of the above deposit is October 16, 2000, which is after the U.S. filing date of this application, and the biological material, which is deposited, is a biological material specifically identified in the application as filed, on page 10, lines 11-12 ("The nucleotide sequence and the translation of the open reading frame of CDMP-1 are presented in Figure 1.").

3. That the name and address of the depository is:
American Type Culture Collection (ATCC)
10801 University Blvd.
Manassas, Virginia 20110, U.S.A.

4. That a statement that the culture(s) deposited with the above named depository was (were) viable and was (were) capable of reproduction, if appropriate, on the date of deposit is attached. Such statement is executed by the depository.

5. That, with respect to the permanence of the culture(s) deposit, the depository is an official depository, in accordance with the Budapest Treaty for the above deposited culture(s). Dr. Moos stated that should the microorganism(s) mutate, become nonviable or be inadvertently destroyed, applicants will replace such microorganism(s) for at least 30 years from the date of the original deposit, or at least 5 years from the

date of the most recent request for release of a sample or for the life of any patent issued on the above-mentioned application, whichever period is longer.

6. That, with respect to availability of the culture(s), Dr. Moos stated that the deposit has been made under conditions of assurance of (a) ready accessibility thereto by the public if a patent is granted whereby all restrictions to the availability to the public of the culture so deposited will be irrevocably removed upon the granting of the patent, with the one exception being that permitted by 37 C.F.R. § 1.808, and (b) access to the culture will be available during pendency of the patent application to one determined by the Commissioner to be entitled under 37 C.F.R. § 1.14 and 35 U.S.C. § 122.

7. That a comparison of the nucleotide (SEQ ID NO:1) and amino acid (SEQ ID NO:2) sequences in USP 5,994,094 to Hotten et al. with the nucleotide (SEQ ID NO:11) and amino acid (SEQ ID NO:13) sequences in PCT/US94/12814 to Applicant appears to reveal that there are 8 different amino acids. It turns out that Applicant's nucleotide (SEQ ID NO:11) and amino acid (SEQ ID NO:13) sequences contain sequencing errors. Correcting for errors, a comparison reveals that the protein-encoding data are identical except for a polymorphism in which the Hotten et al. sequence encodes S (ser) at amino acid position 276 while Applicant's sequence encodes A (ala), due to T (Hotten et al.'s SEQ ID NO:1 at nucleotide position 1465) changed to G (Applicant's SEQ ID NO:11 at nucleotide position 1090). Applicant's nucleotide and amino acid sequences are thus not identical to Hotten et al.'s nucleotide and amino acid sequences because they are polymorphic.

C. Discussion of Teaching Claims

Claims 33-40 are "teaching" claims because they teach the embodiment "at-a-glance." In accordance with the maxim that a patentee may be his own lexicographer (MPEP 608.01(o)), the claims coin the phrase "cartilage-derived morphogenetic protein" (CDMP) and teach at-a-glance that the embodiment is related to a CDMP. In contrast, if the claims simply gave a deposit number, the reader would not know what was being claimed without doing additional research. Moreover, the term "morphogenetic" does not appear in a vacuum but is to be read in the context of a "cartilage-derived morphogenetic protein" (CDMP), thus contributing to rather than detracting from definiteness. Finally, the claims also provide the deposit number, thus precluding any overreaching beyond the scope of enablement. Because they are "teaching" claims, because they further the notice function of claims, and because they are commensurate in scope with the patent specification, the claims are patentable to Applicant.

D. Discussion of PCT/EP/00350 to Neidhardt

The Office Action rejected Claims 27-32 under 35 USC 102(b) as being anticipated by PCT/EP/00350 to Neidhardt. The response is that, according to MPEP 2131, to anticipate a claim, the reference must teach every element of the claim. The reference does not teach every element of amended Claim 27:

> An isolated DNA molecule which codes for a protein of the TGF-β family, wherein said protein comprises a sequence W-I-(I/M/V)-A-P-L-(D/E)-Y-E-A-(Y/F/H)-H-C-E-G-(L/V)-C-(D/E)-F-P-L-R-S-H-L-E-P-T-N-H-A (SEQ ID NO:15), with the proviso that said sequence is not W-I-I-A-P-L-E-Y-E-A-F-H-C-E-G-L-C-E-F-P-L-R-S-H-L-E-P-T-N-H-A (SEQ ID NO:17).

The reason the reference does teach every element of amended Claim 27 is because the reference teaches a protein of the TGF-β family wherein the protein comprises a

sequence W-I-I-A-P-L-E-Y-E-A-F-H-C-E-G-L-C-E-F-P-L-R-S-H-L-E-P-T-N-H-A (page 19, SEQ ID NO:3, amino acid residues 317-347). Amended Claim 27, however, excludes a protein of the TGF-β family wherein the protein comprises a sequence W-I-I-A-P-L-E-Y-E-A-F-H-C-E-G-L-C-E-F-P-L-R-S-H-L-E-P-T-N-H-A (SEQ ID NO:17). Therefore, the reference does not teach every element of amended Claim 27, or Claims 28-32 dependent thereon, and the rejection for anticipation fails.

E. Discussion of Support for Claimed Genus

The Office Action rejected Claims 27-32 under 35 USC 112, first paragraph, as purportedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The response is that, according to MPEP 2163 II A 3 (a) (ii), the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by reduction to drawings or structural chemical formulas that are sufficiently detailed to show that Applicant was in possession of the claimed invention as a whole. Here, reduction to drawings or structural chemical formulas are sufficiently detailed to show that Applicant was in possession of the claimed genus.

According to Example 4, the amino acid sequence similarity between the human CDMP-1 and bovine CDMP-2 proteins had prompted Applicant to further investigate conservation of the CDMPs across different species. Identification of a highly conserved consensus sequence in CDMP proteins proceeded as follows. RNA isolated from chicken sternal cartilage, bovine articular cartilage and human articular cartilage was employed as the template in RT-PCR protocols using two degenerate oligonucleotide primers corresponding to highly conversed motifs in the C-terminal region of BMPs. Genomic DNA isolated from Xenopus and zebrafish was also used as the template for amplification of related gene sequences in a PCR protocol that employed the same primer sets. Amplified DNA fragments were subcloned according

to standard procedures. The inserts from various isolates were sequenced by standard dideoxy chain termination protocols. Aligned segments of the predicted proteins encoded by the cloned cDNAs are presented in Figure 4 (reproduced below):

Xenopus CDMP-x	WI	I	APL	E	YEA	H	HCEG	V	C	D	FP LRSHLEPTNH A	(SEQ ID NO:16)
Human CDMP-1	WI	I	APL	E	YEA	F	HCEG	L	C	E	FP LRSHLEPTNH A	(SEQ ID NO:17)
Chicken CDMP-x	WI	I	APL	E	YEA	Y	HCEG	D	C	E	FP LRSHLEPTNH A	(SEQ ID NO:18)
Zebrafish CDMP-3	WI	V	APL	D	YEA	Y	HCEG	V	C	D	FP LRSHLEPTNH A	(SEQ ID NO:19)
Xenopus CDMP-x	WI	I	APL	E	YEA	Y	HCEG	V	C	D	FP LRSHLEPTNH A	(SEQ ID NO:20)
Human CDMP-2	WI	I	APL	E	YEA	Y	HCEG	V	C	D	FP LRSHLEPTNH A	(SEQ ID NO:21)
Bovine CDMP-2	WI	I	APL	E	YEA	Y	HCEG	V	C	D	FP LRSHLEPTNH A	(SEQ ID NO:22)
Zebrafish CDMP-x	WI	M	APL	D	YEA	Y	HCEG	D	C	D	FP LRSHLEPTNH A	(SEQ ID NO:23)
Consensus	WI	I	APL	E	YEA	Y	HCEG	V	C	D	FP LRSHLEPTNH A	(SEQ ID NO:24)

Results of the protein alignments clearly indicated that CDMP family members from several species shared a common amino acid sequence motif in the region of the proteins encoded by the amplified cDNA segments. Of the 31 amino acid positions presented in Figure 4, all but 5 were occupied by identical amino acid residues for all of the isolates. The variable amino acids were located at positions 3, 7, 11, 16 and 18. Position 3 was occupied either by I, M or V. Position 7 was occupied by either D or E, both of which have acidic side groups. Position 11 was occupied by either Y, F or H. Position 16 was occupied by L or V, and position 18 was occupied by D or E. The consensus deduced from this alignment was:
W-I-(I/M/V)-A-P-L-(D/E)-Y-E-A-(Y/F/H)-H-C-E-G-(L/V)-C-(D/E)-F-P-L-R-S-H-L-E-P-T-N-H-A (SEQ ID NO:15).

In sum, the amino acid sequence similarity between the human CDMP-1 and bovine CDMP-2 proteins had prompted Applicant to further investigate conservation of the CDMPs across different species. In particular, Applicant employed a PCR amplification protocol to isolate CDMP cDNA sequences from a variety of species. Based on alignments of the predicted proteins encoded by these cDNAs, Applicant identified a highly conserved amino acid sequence spanning 31 residues. Only 5

amino acid positions within this sequence showed variability. All remaining positions were identical for all isolates. As disclosed in Example 4, even the 5 variable positions showed a high degree of conservation. Applicant concluded that this structural conservation therefore represented a functional domain that is characteristic of the CDMP family of proteins. Applicant surmised that those of ordinary skill in the art would appreciate that such extraordinary amino acid sequence conservation is indicative of a functional domain. Applicant concluded that the consensus amino acid sequence presented in Example 4 is "critical" to the biological activity of the CDMPs.

The consensus amino acid sequence of SEQ ID NO:15 that Applicant concluded is "critical" to the biological activity of CDMPs shows that the written description requirement for the claimed genus is satisfied through sufficient description of a representative number of species by reduction to drawings or structural chemical formulas that are sufficiently detailed to show that Applicant was in possession of the claimed invention as a whole. According to MPEP 2163 I B, under certain circumstances, omission of a limitation can raise an issue regarding whether the inventor had possession of a broader, more generic invention. This is not a case, however, where a claim omits an element that Applicant describes as an essential or critical feature of the invention originally disclosed. Applicant concluded the consensus amino acid sequence of SEQ ID NO:15 is "critical" to the biological activity of the CDMPs, and the consensus amino acid sequence of SEQ ID NO:15 is not omitted from Claims 27-32.

According to MPEP 2163 II A 3 (a), *Regents of the University of California v. Eli Lilly*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998), holds that, in claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. The consensus amino acid sequence of SEQ ID NO:15 that those of

ordinary skill in the art would appreciate based on such extraordinary amino acid sequence conservation is indicative of a functional domain is such a generic formula.

According to MPEP 2163 II A 3 (a), an applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics that provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics. The consensus amino acid sequence of SEQ ID NO:15 that represents a functional domain as indicated by such a high degree of structural conservation is such a chemical structure.

The Office Action alleges that other than SEQ ID NO:15, other distinguishing structural attributes shared by members of the genus are not indicated, but Applicant concluded that the consensus amino acid sequence of SEQ ID NO:15 is "critical" to the biological activity of CDMPs. According to MPEP 2163 II A 2, *In re Rasmussen*, 211 USPQ 323, 327 (CCPA 1981) holds that "one skilled in the art who read Rasmussen's specification would understand that it is unimportant how the layers are adhered, so long as they are adhered". Similarly, because it is "critical" to the biological activity of CDMPs, what is important here is the consensus amino acid sequence of SEQ ID NO:15. It follows that other distinguishing structural attributes shared by members of the genus are unimportant and need not be indicated to show that Applicant had possession of the claimed genus.

Continuing with MPEP 2163 II A 2, *In re Rasmussen* is to be compared with *Amgen, Inc. v. Chugai Pharmaceuticals Co., Ltd.,* 18 USPQ2d 1016, 1021 (Fed. Cir. 1991), which holds that "it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it". Likewise, here the consensus amino acid sequence of SEQ ID NO:15 is the generic formula that distinguishes the chemical genus from other materials. This is not a case such as described at MPEP 2163 II A 2 where a definition by function alone "does not suffice" to sufficiently describe a coding

sequence "because it is only an indication of what the gene does, rather than what it is." Eli Lilly, 43 USPQ2d at 1406; see also *Fiers v. Revel*, 25 USPQ2d 1601, 1605-06 (Fed. Cir. 1993) (discussing *Amgen, Inc. v. Chugai Pharmaceuticals Co., Ltd.,* 18 USPQ2d 1016 (Fed. Cir. 1991)). Here, in the present case, the definition is not by function alone but is by chemical structure. Nevertheless and contrary to the Office Action alleging that other distinguishing functional characteristics shared by members of the genus are not indicated, an additional definition by function is indicated by the requirement that the protein be a member of the TGF-β family.

According to MPEP 2163 II A 2, structural formulas provide a convenient method of demonstrating possession of specific molecules, but other identifying characteristics or combination of characteristics may demonstrate the requisite possession. Here, in the present case, Applicant need not rely on other identifying characteristics or combination of characteristics that may demonstrate the requisite possession, because Applicant provides the structural formula itself. The structural formula, i.e., the consensus amino acid sequence of SEQ ID NO:15, demonstrates that Applicant had possession of the claimed genus, thus the rejection for lack of written description cannot stand.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 10/8/02

By: _____

Nancy W. Vensko
Registration No. 36,298
Attorney of Record
2040 Main Street, 14th Floor
Irvine, CA 92614
(805) 547-5585

VERSION WITH MARKINGS TO SHOW CHANGES MADE

On this set of pages, the insertions are double underlined while the ~~deletions are struck through~~.

In the claims:

27. (Amended) An isolated DNA molecule which codes for a protein of the TGF-β family, wherein said protein comprises a sequence W-I-(I/M/V)-A-P-L-(D/E)-Y-E-A-(Y/F/H)-H-C-E-G-(L/V)-C-(D/E)-F-P-L-R-S-H-L-E-P-T-N-H-A (SEQ ID NO:15) , with the proviso that said sequence is not W-I-I-A-P-L-E-Y-E-A-F-H-C-E-G-L-C-E-F-P-L-R-S-H-L-E-P-T-N-H-A (SEQ ID NO:17).

In the specification, please amend page 10, paragraph 1, as follows.

Thus, cloned inserts having novel BMP-like sequences were isolated, radiolabeled and used to screen both human and bovine articular cartilage cDNA libraries. Six clones were isolated from the human cDNA library. The sizes of the EcoRI inserts (2.1 kb) and their restriction maps were found to be identical for all six clones. One clone was used for nucleotide sequencing. An open reading frame encoding a BMP related protein, designated CDMP-1, was identified. It appeared that the human cDNA clone lacked the coding region for the first methionine and signal peptide. The 5' end of the human CDMP-1 was subsequently obtained from a human genomic clone isolated from a library constructed in the EMBL-3 vector (Clontech, Palo Alto, CA). The 5' end of human CDMP-1 contained a consensus translation initiation sequence disclosed by Kozak (*J. Biol. Chem.* **266**:19867 (1991)) immediately followed by a putative transmembrane signal sequence described by Von Heijne (*Nucl. Acids*

Res. **14**:4683 (1986)). The nucleotide sequence and the translation of the open reading frame of CDMP-1 are presented in Figure 1 and deposited at American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, Virginia 20110, USA, as PTA-2595, on October 16, 2000. As shown in the figure, the CDMP-1 protein was predicted to have 500 amino acids, to consist of a pro-region of 376 amino acids, a typical cleavage site (Arg-Xaa-Xaa-Arg/Ala) (SEQ ID NO:9), and a C-terminal domain of 120 amino acids containing the seven highly conserved cysteines characteristic of the TGF-β gene family. A single N-linked glycosylation site is located in the pro-region (marked by an asterisk in the figure). A putative signal peptide is underlined in bold. A termination codon (TGA) is shown in the 5' untranslated region. The bold dashed underline indicates the fragment obtained by RT-PCR that was subsequently used to screen cDNA libraries. The 13 amino acid peptide used to raise polyclonal antibodies in rabbits is underlined. A vertical arrowhead marks the boundary between the sequence obtained from genomic DNA and cDNA.